REMARKS

Claims 24, 36, 43 and 44 have been amended. The amendments clarify that the allergen is expressed in the bacterial cell while the bacterial cell is in the subject. Thus, the mode of expression is prokaryotic, unlike the mode of expression used in U.S. 5,958,891 ("Hsu et al." in the Office Action; the '891 patent, herein). In the accompanying declaration, Dr. Hsu, one of the named inventors, explains the differences between prokaryotic and eukaryotic expression and the implications of these differences.

The Examiner has rejected claims 24, 25, 28-33, and 43 as obvious in view of the '891 patent and Medaglini. The remaining claims are also rejected as obvious in view of a combination of references that include the '891 patent and Medaglini. However, as Dr. Hsu explains in his Declaration, the contents of which are incorporated by reference herein, there is no motivation to combine the '891 patent and Medaglini. Further, there is no expectation for success for the alleged combination since both references provide evidence to the contrary.

The Applicants first address particular points raised by the Examiner. The Examiner asserts, on pages 5-6 of the Office Action dated April 9, 2003, that:

> Medaglini *et al*. teach a general system that allows for the stable expression of a wide range of protein antigens on the surface of non-pathogenic Gram-positive commensal bacteria. The exemplified embodiment is Streptococcus gordonii engineered to surface expressing an allergen from hornet venom (M6 protein). They teach that the advantage of their system is using a bacteria that is live and non-pathogenic, yet maintaining certain invasive/adherence qualities to induce an immune response (Introduction, page 6868), they teach the system has a general applicability for deliver foreign antigens to a mammalian host because the prolonged exposure of the immune system to a recombinant antigen achieved by the stable colonization of a recombinant commensal is a safe and efficient way of overcoming the need for repeated doses of antigen (paragraph bridging left and right columns in page 6872. The exemplified production of antigen-specific IgA and IgG is "as a proof of the general applicability " (first paragraph, right column, page 6868).

The Applicants respectfully submit that Medaglini's system is more limited. Medaglini describes the system as follows:

> [W]e have developed a system whereby nonpathogenic Gram-positive commensal bacteria that occupy a specific mucosal niche may be used to stimulate a mucosal immune response against a pathogen that enters the mammalian host at a specific site (oral, intestinal, or vaginal).

> In our model system, we genetically removed nearly all of the surface exposed region of the M6 protein of *Streptococcus pyogenes* and replaced it with a foreign antigen, retaining the C-terminal attachment motif of the M6 protein. The strain Challis of *Streptococcus gordonni*, a human oral commensal bacterium, was chosen as the vector organism. As proof of the general applicability of the system, Ag5.2 . . . was expressed on the surface of *S. gordonni.*

(p. 6868, Medaglini; reference omitted, emphasis added)

Medaglini's reference to the general applicability of the system clearly refers back to the system for "stimulat[ing] a mucosal immune response." Thus, Medaglini does not stand for the more general proposition alleged by the Examiner.

The Examiner further asserts, on page 6 of the Office Action dated April 9, 2003, that:

> The exemplified production of antigen-specific IgA and IgG is "as a proof of the general applicability " (first paragraph, right column, page 6868). Therefore, the system does not conflicting with the method of Hsu et al, only enhancing the efficiency of delivered nucleic acids. [emphasis added]

However, Medaglini does conflict with the '981 patent. Production of antigen-specific IgA and IgG is contrary to the suppression of IgE as required by the methods of claims 24, 36, and 43. See also paragraphs 18 and 19 of Dr. Hsu's declaration.

The Examiner also asserts, on page 6 of the Office Action dated April 9, 2003, that:

> Therefore, the system does not conflicting with the method of Hsu et al, only enhancing the efficiency of delivered nucleic acids. Applicants are reminded that Medaglini et al reference is relied upon for general application of using live gram-positive bacteria as a nucleic acid delivery vehicle, which would enhance the immune response of the nucleic acid that they carried on. [emphasis added]

The Applicants are unclear as to how Medaglini is used as a nucleic acid delivery vehicle. As Dr. Hsu observes in paragraph 15 of his Declaration, Medaglini does not suggest the radical position that *Streptococcus gordonii* could be used to delivery a nucleic acid encoding an antigen from the *S. gordonii* bacterium into a eukaryotic cell of a subject so that the eukaryotic cell would express the nucleic acid and produce the antigen. Further the Examiner proposes that such a nucleic acid delivery vehicle would "enhance the immune response." However, an enhanced immune response is contrary to a method of suppressing IgE production as required by the method of claims 24, 36, and 43.

Regarding the general combination of the '891 patent and Medaglini, the Applicants first note that there is no motivation to combine the '891 patent and Medaglini. The '891 patent uses eukaryotic expression and presentation of antigens on MHC class I molecules to suppress IgE production. Paragraphs 10 to 12 of Dr. Hsu's Declaration discuss the '891 patent. Medaglini uses prokaryotic expression to enhance immunoglobulin production. Paragraphs 13 to 15 of Dr. Hsu's Declaration discuss Medaglini . The Examiner is also referred to paragraphs 6 to 8 of Dr. Hsu's Declaration for an explanation of differences between eukaryotic and prokaryotic expression.

As explained by Dr. Hsu in paragraph 17 of the declaration, Medaglini does not teach a nucleic acid delivery vehicle for introducing nucleic acids into eukaryotic cells. Thus, there is no basis for an alleged motivation (see, e.g., lines 7 and 18, page 6 of the Office Action dated April 6, 2003) that the Gram-positive commensal bacteria of Medaglini could be used as a "nucleic acid delivery vehicle" to transfer nucleic acid from the bacterium into a eukaryotic cell so that the nucleic acid can be expressed in the eukaryotic cell as taught by the '891 patent.

As explained by Dr. Hsu in paragraphs 18 and 19 of the declaration, Medaglini and the '891 patent include very contrasting teachings. Some differences are summarized in the following table:

	Medaglini	The '891 Patent
Agent	Commensal bacterium	Injected Nucleic acid
Mode of Expression	Prokaryotic	Eukaryotic
Mode of Ag Display	[not discussed]	Class I MHC
Result	Enhanced immunoglobulin production	Suppressed immunoglobulin (IgE) production
Proposed Mechanism	Agent stimulates Mucosal Immune Response	MHC presented antigens induce CD8+ T cells production of IFN-γ to suppress immunoglobulin production

The five criteria in the table above are central features of both references. At least with respect to these five criteria, there is no common ground between the two references.

The two references teach away from each other. First, one skilled in the art, when seeking to suppress immunoglobulin production, would not turn to a system that enhances immunoglobulin production. Second, one seeking to exploit the teachings of the '891 patent,

which describes presenting antigens on class I MHC molecules after antigen expression in eukaryotic cells, would not turn to a prokaryotic expression system. Prokaryotic expression is not known to result in antigen presentation on class I MHC molecules since production of the antigen in a eukaryotic cell is typically required for presentation on class I MHC molecules.

Thus, there is no motivation to combine the '891 patent and Medaglini.

Even if one were to assume such a motivation, there is no expectation of success for the alleged combination. Paragraphs 20-23 of Dr. Hsu's declaration explain that both the '891 patent and Medaglini provide evidence that controvert the expectation of success. The evidence in the '891 patent suggests that eukaryotic expression of allergens is important to immunoglobulin suppression and the evidence in Medaglini suggests that prokaryotic expression results in immunoglobulin enhancement. This evidence refutes the obviousness rejection made by the Examiner.

The Applicants respectfully submit that all rejections based on the combination of the '891 patent and Medaglini should be withdrawn in view of the above arguments and the Declaration of Dr. Hsu. Because all pending claims are rejected in view of some combination of the '891 patent and Medaglini, the Applicants respectfully submit that all claims are now in condition for allowance.